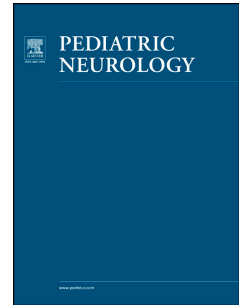




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



The outcome of COVID-19 in Pediatric Onset Multiple Sclerosis Patients

Ibrahim Oncel, Nurettin Alici, Ismail Solmaz, Dogan Dinc Oge, Yasemin Ozsurekci, Banu Anlar

PII: S0887-8994(22)00107-2

DOI: <https://doi.org/10.1016/j.pediatrneurol.2022.06.004>

Reference: PNU 10148

To appear in: *Pediatric Neurology*

Received Date: 7 December 2021

Revised Date: 18 May 2022

Accepted Date: 4 June 2022

Please cite this article as: Oncel I, Alici N, Solmaz I, Oge DD, Ozsurekci Y, Anlar B, The outcome of COVID-19 in Pediatric Onset Multiple Sclerosis Patients, *Pediatric Neurology* (2022), doi: <https://doi.org/10.1016/j.pediatrneurol.2022.06.004>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Elsevier Inc. All rights reserved.

The outcome of COVID-19 in Pediatric Onset Multiple Sclerosis Patients

Ibrahim Oncel^{a*}, Nurettin Alici^a, Ismail Solmaz^{a1}, Dogan Dinc Oge^b, Yasemin Ozsurekci^c,
Banu Anlar^a

^a Department of Pediatric Neurology, Hacettepe University Faculty of Medicine, Ankara,
Turkey

^b Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey

^c Department of Pediatric Infectious Disease, Hacettepe University Faculty of Medicine,
Ankara, Turkey

¹ **Current address:** Dr. Sami Ulus Children's Hospital, Pediatric Neurology Clinic, Ankara,
Turkey

Running title: COVID-19 in Pediatric Onset MS

Word count: Abstract: 299; Main text: 1998

***Corresponding author:** Ibrahim Oncel

Address: Hacettepe University Children's Hospital, Department of Pediatric Neurology,
06230, Ankara, Turkey

Phone: +903123051165

Fax: +903123053284

e-mail: dribrahimoncel@gmail.com

Abstract**Background**

The pathogenesis of multiple sclerosis (MS) involves immune-mediated mechanisms, and disease-modifying therapies (DMTs) administered in MS have immunomodulatory effects. The concern about MS patients' susceptibility to coronavirus disease 2019 (COVID-19) has prompted several studies based on clinical observations and questionnaires. Information about COVID-19 in pediatric-onset multiple sclerosis (POMS) is scarce.

Objective

Collecting information on the experience of POMS patients with COVID-19 during the pandemic.

Methods

This cross-sectional study was conducted with POMS patients diagnosed at Hacettepe University Pediatric Neurology Department and under 23 years of age between October 1 and December 31, 2021. Those who experienced COVID-19 or had a history of contact and were found seropositive for COVID-19 were evaluated for the severity of COVID-19, disability, treatment status and comorbidities.

Results

Among the 101 POMS patients, 13 reported having had COVID-19 and five who were exposed and seropositive but clinically asymptomatic. Of these 18 patients, 14 were ≤ 18 years of age at the time of the study. All 13 patients (72%) reported mild symptoms without hospitalization or respiratory support. Four/18 had a neurological disability (expanded disability status scale (EDSS) scores ranging between 1-7.5), while the remaining had a score of 0. The outcome of COVID-19 was not affected by DMT, neurological disability and comorbidity.

Conclusion

In this single-center POMS series, the small subgroup of patients who had contacted the SARS-CoV-2 virus or developed COVID-19 had reported no or mild symptoms. This may be partly related to the infrequent use of rituximab in this group. Our results corroborate those in adult-onset MS where no increased risk is reported for patients whose EDSS scores are <6 and who are not on B cell depleting DMTs. Although less frequently than in adult MS, immunosuppressive DMTs may be needed in POMS; therefore, the importance of appropriate vaccination is to be underlined.

64 **Key words:** pediatric onset multiple sclerosis, COVID-19, severity, disease modifying
65 therapy

Introduction

Autoimmune disorders are characterized by inflammatory reactions due to immune dysregulation and loss of self-tolerance. Multiple sclerosis (MS) is an autoimmune disorder where disease modifying therapies (DMTs) also affect the immune system at various levels. Their immunomodulatory effects include reducing lymphocyte proliferation, depleting B lymphocytes, blocking the entry of lymphocytes into the central nervous system (CNS), or preventing lymphocyte egression from lymph nodes. Therefore, the disorder and its treatments can create a source of concern for patients and their physicians particularly regarding the risk for SARS-CoV-2 infection and a severe course of COVID-19. For this reason, caution about prescribing DMTs had been discussed early in the pandemic. Evidence on the outcome of COVID-19 among MS patients receiving DMTs has been accumulating in the last 2 years and provided some confidence in their use in the general MS population so far. However, the heterogeneity of patients, the existence of special subpopulations, and the diversity of therapies require data from larger cohorts. In particular, information on pediatric onset patients is scarce.

Pediatric-onset MS (POMS) accounts for 3-10% of all MS cases. The management of POMS patients is mostly based on data and experience from adult MS series. This represents a challenge for pediatric neurologists because of certain characteristics of MS in the young age group such as more active inflammation, higher relapse rate, and differences in the immune system in childhood [1].

Despite the observation of the SARS-CoV-2 virus generally causing a milder disease in children compared to adults, children with chronic neurological conditions like MS, particularly those under immunomodulatory treatments, deserve special attention during the pandemic. Currently, data on COVID-19 in POMS patients treated with DMTs is limited. The aim of this study was to evaluate the characteristics and outcomes of COVID-19 in POMS patients.

Materials and methods

Study population

We conducted a cross-sectional study between October 1 and December 31, 2021 with patients who had been diagnosed with MS in the Pediatric Neurology Department of Hacettepe University before 18 years of age. Those currently followed in adult neurology

clinics and still under the age of 23 years were also included. Information about COVID-19 infection or exposure during the pandemic was collected from patients or their parents.

None of the patients included in the study had been vaccinated against SARS-CoV-2 virus at the time of evaluation. Ethical approval was obtained from Hacettepe University Clinical Research Ethics Board (2021/23-23).

Data collection

A standardized short questionnaire was given during all routine clinical visits or by phone call. Those who gave a history of having been diagnosed with COVID-19 by real-time polymerase chain reaction (RT-PCR) test were further queried using a more detailed datasheet. Any positive RT-PCR test reports were obtained from patients or parents. Patients who reported exposure to COVID-19 but had not been tested by RT-PCR were advised to take a serum antibody test. Those who tested seropositive were also queried using the same datasheet. Demographic and clinical data, duration of disease, last available expanded disability status scale (EDSS) scores, treatments in the last 3 months and comorbidities were recorded from the hospital registry and confirmed by phone. Descriptive statistics were used to summarize the data.

Severity of COVID-19

The severity of COVID-19 was categorized as defined by Dong et al. [2] based on the clinical characteristics, laboratory and radiological findings as follows: (a) asymptomatic infection: no clinical or radiological signs despite the positive RT-PCR test, (b) mild disease: acute upper respiratory tract infection symptoms without pneumonia, (c) moderate disease: clinical or radiological pneumonia, (d) severe disease: progressive respiratory difficulty, dyspnea, hypoxia, central cyanosis, (e) critical disease: acute respiratory distress syndrome (ARDS), shock, and organ dysfunction.

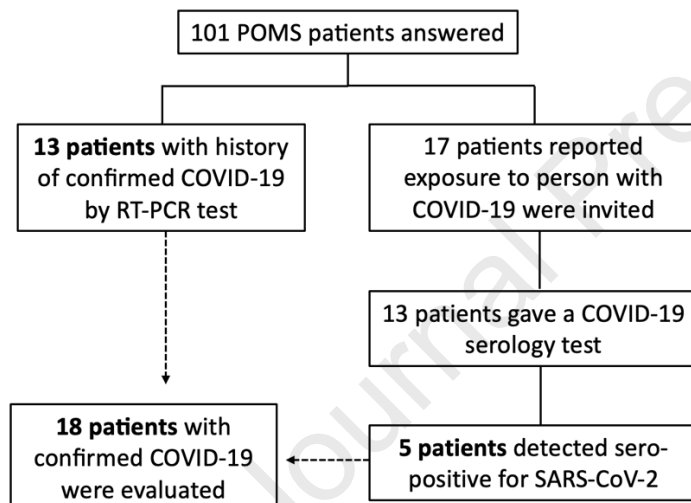
Results

A total of 101 patients with POMS, F/M 67/34, age 9-23 (mean 18.7) years were being followed in our clinic during the period of the study. The duration of MS was 4-96 (mean 45) months. All had the relapsing-remitting form of MS. Their treatments consisted of interferon-beta (n=23), teriflunomide (n=17), dimethyl fumarate (n=15), fingolimod (n=9), ocrelizumab (n=8), glatiramer acetate (n=3), cladribine (n=2) and corticosteroid (n=1). Twenty-three

patients were not under treatment at the time of the study because of recent referral, search for a second opinion, adverse effects of the previously prescribed DMT, use of alternative treatments, or personal preference. Two patients had discontinued their treatment at the beginning of the pandemic because of concern about immunosuppression.

In total 18/101 patients (17.8%) aged between 9-22 years (F/M:11/7) had a confirmed COVID-19 infection diagnosed either by RT-PCR test (n=13) or serology (n=5) during the defined period (**Figure 1**). In COVID-19 RT-PCR positive patients the average time from the acute illness to reporting of COVID-19 symptoms was 3.1 months (0-10 months). Fourteen out of 18 patients were ≤ 18 years; all had relapsing-remitting MS.

Figure 1. Flowchart for patients included in the study



POMS; pediatric-onset multiple sclerosis, RT-PCR; real-time polymerase chain reaction

Among 18 patients included in the study, most had no disability (EDSS scores 0) except in four cases that had EDSS scores from 1 to 7.5. A comorbid condition was present in four patients: 1 had obesity, 1 had familial Mediterranean fever, 1 had acute rheumatic fever, and 1 had cardiac arrhythmia. (Table, cases 2,3,5,10).

COVID-19 infection was asymptomatic in 5 patients and mildly symptomatic in 13 patients. Confirmation in these groups was by serology and RT-PCR respectively (Table). None had pneumonia or had been hospitalized for COVID-19. Common symptoms were fatigue (n=6), fever (n=5), cough (n=5), sore throat (n=2), anosmia (n=5), ageusia (n=4), myalgia (n=3) and arthralgia (n=1). The median duration of symptoms was 3 days (1-15 days): the longest was

anosmia in one patient (15 days). Neurological symptoms reported by 7 patients consisted of headache, anosmia and ageusia (Table).

Table. Demographic and clinical characteristics of pediatric-onset multiple sclerosis patients with confirmed COVID-19

Patient	Age / Sex	Duration of MS (months)	EDSS score	DMT	Comorbidity	COVID-19 severity	Symptoms	Method for COVID-19 diagnosis
1	17 / F	9	0	IFN	None	Mild disease	Cough, fatigue	RT-PCR
2	9 / F	4	0	None*	FMF	Mild disease	Fever, fatigue	RT-PCR
3	20 / F	56	3	TFM	ARF	Mild disease	Headache, fatigue, cough, anosmia	RT-PCR
4	16 / M	50	0	IFN	None	Asymptomatic	None	Serology
5	18 / M	40	0	None [#]	Obesity (BMI:33.3)	Mild disease	Fever, fatigue	RT-PCR
6	15 / M	15	0	TFM	None	Asymptomatic	None	Serology
7	18 / F	14	0	DMF	None	Asymptomatic	None	Serology
8	18 / M	11	2	None [#]	None	Mild disease	Headache, arthralgia, fatigue	RT-PCR
9	18 / M	31	7.5	OCZ	None	Mild disease	Fever, sore throat	RT-PCR
10	22 / F	58	0	TFM	Cardiac arrhythmia	Mild disease	Sore throat	RT-PCR
11	20 / F	71	1	DMF	None	Mild disease	Myalgia, anosmia, ageusia	RT-PCR
12	16 / F	18	0	IFN	None	Mild disease	Anosmia	RT-PCR
13	19/F	43	0	None [#]	None	Mild disease	Myalgia, fatigue	RT-PCR
14	13/F	11	0	DMF + IFN	None	Asymptomatic	None	Serology
15	17/F	26	0	DMF	None	Asymptomatic	None	Serology
16	15/M	96	0	FNG	None	Mild disease	Cough, anosmia, ageusia	RT-PCR
17	17/M	4	0	None*	None	Mild disease	Fever, ageusia, cough, headache	RT-PCR
18	18/F	95	0	DMF	None	Mild disease	Fever, cough, myalgia, anosmia, ageusia	RT-PCR

EDSS; expanded disability status score, DMT; disease modifying therapy, IFN; interferon-beta, TFM; teriflunomide, DMF; dimethyl fumarate, OCZ; ocrelizumab, FNG; fingolimod, FMF; familial mediterranean fever, ARF; acute rheumatic fever, BMI; body mass index, RT-PCR; real-time polymerase chain reaction

*Recent referral, DMT was started after recovery from COVID-19

[#] Declined all recommended available DMTs.

Discussion

During the pandemic, POMS patients continued their treatment without interruption or dose alteration, as described in guidelines for MS [3]. All POMS patients were advised to strictly comply with the health authorities' recommendations for protection during the pandemic. However, the fact that both MS and its treatment can increase the risk and severity of a COVID-19 infection has constituted as a source of concern for patients since the beginning of the pandemic. Recent multicentric studies with large cohorts of adult MS patients showed older age, male sex, long disease duration, higher EDSS and recent use of corticosteroids to be associated with severe COVID-19 while DMTs were safe in COVID-19 except for anti-CD20 monoclonal antibodies, notably rituximab [4,5]. However, studies on POMS are scarce. To date, only two studies reported on COVID-19 in POMS. Parotta et al's study of 76 MS patients diagnosed with COVID-19 included nine POMS patients of whom two were hospitalized for the need of supplemental oxygen. Neither required invasive ventilation [6]. The other study reported 26 POMS patients on natalizumab of whom none contracted COVID-19, suggesting no increase in the risk of COVID-19 is expected under this treatment [7].

Our study included patients up to 23 years because they were still under the follow-up of our department during transition to adult clinics; 14 patients were ≤ 18 years of age. Those who had COVID-19 infection had a mild disease lasting for 2-15 days. The remaining five patients had asymptomatic infection confirmed by serum antibody testing. None of the cases required hospitalization, including 13 who were on DMT. Except for interferons and glatiramer acetate, DMTs used in the treatment of MS suppress immunity to various degrees, and 10 of our patients were receiving such drugs [8]. In an ongoing study of POMS and pediatric clinically isolated syndrome cases whose outcomes have not been reported yet, 18 patients had confirmed or highly suspected COVID-19, and 4 were hospitalized; three of them were on rituximab treatment [9]. Anti-CD20 monoclonal antibody treatments have been related to worse clinical outcomes of COVID-19 in MS [5]. We had only one patient (case 9) on anti-CD20 therapy, ocrelizumab, and thus have insufficient data to draw a conclusion about this relationship in POMS.

The presence of comorbidities, especially obesity and cardiovascular disease is associated with more severe COVID-19 in adult MS patients [4]. Neurological disability may also increase the risk of severe COVID-19: in a recent Morbidity and Mortality Weekly Report by

the CDC, 14% of hospitalized patients aged between 12 and 17 had a neurological comorbidity [10,11]. Advanced disability (EDSS ≥ 6) in MS has been described as an independent risk factor for severe COVID-19 disease in a large registry of adult patients [8]. In our cohort, 4/18 patients (22%) with confirmed COVID-19 who had a comorbidity and 4/18 patients (22%) with neurological disability, including one patient with an EDSS of 7.5, had mild COVID-19.

Another question is the effect of the infection on the course of MS. Viral infections may trigger relapses of autoimmune diseases [12]. However, a previous study found no increase in MS relapses after contracting COVID-19 [13]. In line with that, none of the patients in our cohort had experienced a relapse in the three months following COVID-19.

There are several limitations of this study. We collected data from patients diagnosed with COVID-19 by RT-PCR test and those who were found seropositive after a history of exposure. Seropositive patients who were not aware of exposure or did not undergo an antibody test may have been missed. Information about the contact, diagnosis, or clinical characteristics of COVID-19 infection was based on history and self-reports, and therefore may be incomplete. The time lag between COVID-19 infection and our study may also bring a recall bias. Our sample size did not permit an analysis for any individual risk factors, or the effect of specific DMTs on disease course. Our study covered a particular time window: the emergence of new variants of the virus by the time of publication was inevitable. Changes in the virulence of the virus and the regulations for vaccine application now to include ages as young as 12 years in some countries alter the epidemiology of the disease. The availability and choices of DMTs also vary in different countries. Therefore, risk groups may differ between studies. Larger and multiple series are needed to analyze the effects of younger age, comorbidities, treatments, or environment, and identify procedures to minimize the risks of infection.

Declaration of interest: none

References

1. McKay KA, Hillert J, Manouchehrinia A. Long-term disability progression of pediatric-onset multiple sclerosis. *Neurology*. Jun 11 2019;92(24):e2764-e2773. doi:10.1212/WNL.00000000000007647
2. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. Jun 2020;145(6)doi:10.1542/peds.2020-0702
3. Society NM. Global COVID-19 advice for people with MS. Accessed 06.10.2021, 2021. <http://www.msif.org/wp-content/uploads/2021/06/June-2021-MSIF-Global-advice-on-COVID-19-for-people-with-MS-FINAL.pdf>
4. Salter A, Fox RJ, Newsome SD, et al. Outcomes and Risk Factors Associated With SARS-CoV-2 Infection in a North American Registry of Patients With Multiple Sclerosis. *JAMA Neurol*. Jun 1 2021;78(6):699-708. doi:10.1001/jamaneurol.2021.0688
5. Sormani MP, De Rossi N, Schiavetti I, et al. Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis. *Ann Neurol*. Apr 2021;89(4):780-789. doi:10.1002/ana.26028
6. Parrotta E, Kister I, Charvet L, et al. COVID-19 outcomes in MS: Observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. *Neurol Neuroimmunol Neuroinflamm*. Sep 2020;7(5)doi:10.1212/NXI.0000000000000835
7. Margoni M, Gallo P. Natalizumab safety in paediatric-onset multiple sclerosis at the time of SARS-Cov-2 pandemic. *Mult Scler J Exp Transl Clin*. Oct-Dec 2020;6(4):2055217320966346. doi:10.1177/2055217320966346
8. Louapre C, Collongues N, Stankoff B, et al. Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. *JAMA Neurol*. Sep 1 2020;77(9):1079-1088. doi:10.1001/jamaneurol.2020.2581
9. Schreiner, T. (2021, April 17-22). Demographic and Clinical Profile of Pediatric Patients With Multiple Sclerosis With SARS-CoV2 [Poster presentation]. 73rd AAN Annual Meeting, Virtual Meeting. <https://www.aan.com/MSA/Public/Events/Details/13778>
10. Havers FP, Whitaker M, Self JL, et al. Hospitalization of Adolescents Aged 12-17 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1, 2020-April 24, 2021. *MMWR Morb Mortal Wkly Rep*. Jun 11 2021;70(23):851-857. doi:10.15585/mmwr.mm7023e1
11. Barzegar M, Mirmosayyeb O, Gajarzadeh M, et al. COVID-19 Among Patients With Multiple Sclerosis: A Systematic Review. *Neurol Neuroimmunol Neuroinflamm*. Jul 2021;8(4)doi:10.1212/NXI.0000000000001001
12. Etemadifar M, Sedaghat N, Aghababaei A, et al. COVID-19 and the Risk of Relapse in Multiple Sclerosis Patients: A Fight with No Bystander Effect? *Mult Scler Relat Disord*. Mar 20 2021;51:102915. doi:10.1016/j.msard.2021.102915
13. Houen G, Trier NH, Frederiksen JL. Epstein-Barr Virus and Multiple Sclerosis. *Front Immunol*. 2020;11:587078. doi:10.3389/fimmu.2020.587078

Highlights

- Concerns about MS and DMT increasing risks of infection and inflammation prompted this study
- COVID-19 was asymptomatic or mild in pediatric-onset multiple sclerosis (POMS) patients.
- We did not observe any severe cases of COVID-19 in our POMS cohort.